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Atypical Hyperplasia in the Era of Stereotactic Core Needle Biopsy

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Background and Objectives: To characterize both atypical hyperplasia (AH) and the malignancies typically present at open surgical biopsy in women diagnosed with AH by stereotactic core needle biopsy (SCNB).
Methods: Patients with AH diagnosed by SCNB were advised to undergo surgical biopsy to rule out an associated malignancy. Mammography findings, pathology reports and follow-up data were analyzed.
Results: AH was identified by SCNB in 38 of 893 (4.3%) patients. Carcinoma was identified in 12 of 33 (36.4%) patients who went on to surgical biopsy. Ductal carcinoma in situ (DCIS) was present in 11 of the 12 patients with malignancy. There were no characteristic mammographic findings which would identify patients with carcinoma.
Conclusions: When SCNB returns a diagnosis of AH there is a substantial risk of an associated malignancy in the breast. There appear to be no definitive criteria to distinguish which patients harbor a malignancy, and surgical biopsy should always serve as an adjunct diagnostic procedure.

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KEY WORDS: hyperplasia; breast; neoplasm; stereotactic biopsy

INTRODUCTION

Stereotactic core needle biopsy (SCNB) has revolutionized our approach to suspicious breast lesions noted on mammography. In the past, open surgical biopsy was necessary to rule out a malignancy in patients with a suspicious lesion on mammogram. SCNB can effectively rule out cancer with a simple needle biopsy, alleviating the cost and discomfort of surgery. SCNB histologic findings are in agreement with surgical biopsy in over 95% of cases [1]. However there appears to be a high incidence of discordance of surgical results when a diagnosis of atypical hyperplasia (AH) is rendered by SCNB. The prevalence of carcinoma at surgical biopsy after a diagnosis of AH by SCNB has recently been reported to be from 33% to 87% [2–6]. This has led to the emphasis of a follow-up open surgical biopsy in these cases to rule out an associated malignancy. We conducted a prospective study to characterize those patients with AH in an attempt to predict which patients may likely have an associated malignancy and to further define the malignancies. A greater understanding of the prevalent carcinomas present in this situation will assist the surgeon in counseling the patient, planning the appropriate surgical approach and anticipating the outcome.

MATERIALS AND METHODS

Selection for Core Biopsy

All mammograms at Madigan are reviewed by a staff radiologist. As part of our institution's breast pathway,

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mammograms felt to have suspicious lesions are referred to a weekly combined radiology/surgery/oncology/pathology conference for review and evaluation for surgical biopsy, stereotactic core biopsy or observation with appropriate follow-up. Suspicious lesions were classified according to the following: mass without calcifications, mass with calcifications, or calcifications without a mass. Palpable lesions were generally referred for open biopsy unless the patient was a poor surgical candidate and core biopsy might have negated the need for open biopsy. Nonpalpable masses were considered for core biopsy if they appeared suspicious for malignancy based on evidence of irregular appearance, architectural distortion, or margins which appeared indistinct, obscured, or spiculated. Suspicious calcifications considered for core biopsy were classified as amorphous and indistinct, branching (high nuclear grade), pleomorphic (intermediate nuclear grade), round and indistinct (low nuclear grade), dystrophic, or fine. Calcifications not considered to be suspicious and therefore, in general, not meriting core biopsy included punctate, round, eggshell, vascular and spherical patterns [7]. As part of the inceptive design of the breast pathway at Madigan, all patients with nonpalpable suspicious lesions on mammography were referred for core biopsy as opposed to wire localized surgical biopsy as an initial diagnostic step. All core biopsies were performed within the Department of Radiology by a staff radiologist.

Core Biopsy Technique

SCNB was performed using a Lorad ABC dedicated stereotactic breast biopsy table with patients in the prone position. A 14-gauge gun with 23 mm excursion was utilized. Stereotactic views were obtained and coordinates entered into a computer for accurate biopsy. The skin was anesthetized with local anesthetic and a small skin incision was made for insertion of the biopsy needle. The protocol called for five cores from solid lesions and nine cores from clustered microcalcifications. Needle extended images were obtained to confirm accuracy of all biopsies. Additional cores were taken if radiography did not confirm retrieval of calcifications in question.

Surgical Biopsy and Histology

All patients found to have AH (inclusive of atypical lobular or ductal hyperplasia) were advised to undergo open surgical biopsy. Open procedures consisted of a wire localized lumpectomy, typically using a single guide wire placed into the suspicious lesion by stereotactic technique. Open biopsy results were compared with SCNB results for histologic agreement. AH, ductal carcinoma in situ (DCIS) and hyperplasia without atypia were diagnosed by the cytologic and architectural criteria outlined by Page and Anderson [8]. The criteria for the diagnosis of DCIS require a uniform population of cells, round hyperchromatic nuclei with random placement, and the presence of such cells completely involving at least two duct spaces. Conformity to one of the accepted patterns of DCIS was also recognized. Those lesions that met some but not all of the cytologic and architectural criteria for DCIS were diagnosed as AH. Lesions meeting criteria for DCIS that did not involve two spaces were also classified as AH. DCIS lesions were graded as low, medium or high grade. Low grade lesions have small uniform nuclei with fine chromatin and inconspicuous nucleoli. High grade lesions show nuclei with marked variation in size and shape with some large and occasionally bizarre nuclei present. They have course and clumped chromatin and conspicuous nucleoli which may be multiple. Moderate grade lesions are between these extremes, with some cell to cell variation in size and shape and obvious, usually single, nucleoli. Hyperplasia without atypia was defined according to criteria outlined by Page and Anderson [8] as well. Mild hyperplasia is defined as ducts with a three to four cell thickness above the basement membrane, without bridging or distention of the ducts. Moderate and florid hyperplasia are differentiated only by degree, with cellular hyperplasia manifested by at least five cell layers above the basement membrane and evidence of bridging and distention of the ducts, with those features present to a greater degree in florid hyperplasia than in moderate. There must also be no evidence of cytologic atypia or other criteria that would be defined as DCIS. All cases of AH and DCIS were reviewed by two staff pathologists and lesions still in question were forwarded to the Armed Forces Institute of Pathology (AFIP) for consultation. Negative margins were not required on those patients with a primary diagnosis of AH after surgical biopsy.

Follow-up

Patients found to have AH as a primary diagnosis after surgical biopsy continued to be followed in our high risk breast clinic. This includes follow-up physical exam every 6 months and a yearly mammogram. Patients found to have a primary diagnosis of mild to florid hyperplasia without atypia did not undergo surgical biopsy and were referred back to primary care providers for yearly follow-up with yearly mammograms as appropriate according to American Cancer Society guidelines. Patients did not routinely undergo repeat SCNB solely on the history of AH unless there was a change in their mammogram prompting a repeat biopsy.

RESULTS

Screening

From March 1993 through July 1996, 31,390 mammograms were completed at our institution. Approximately half of these were considered diagnostic, completed for a specific concern. The other half were con-

TABLE I. Mammography Results of Patients With AH Found by SCNB

	Mammographic description				
Final pathology[a]	Amorphous and indistinct	Pleomorphic	Branching	Course	Round
AH	5	11	0	0	5
DCIS	0	4	1	0	2
IC	0	0	0	1	0
Total	5	15	1	1	7

[a]AH, atypical hyperplasia; DCIS, ductal carcinoma in situ; IC, infiltrating carcinoma.

sidered screening, completed as a routine exam without a particular antecedent concern. SCNB was performed on 893 patients for suspicious lesions. Specific lesions prompting core biopsy included 346 for suspicious calcifications, 345 for a mass, 62 for a mass with associated calcifications, 44 for a spiculated mass, 16 for asymmetric density, 9 for architectural distortion, and 71 not otherwise specified. AH was diagnosed in 38 patients. Thirty-three patients agreed to undergo open surgical biopsy. Table I shows the patterns of microcalcifications present for all patients with AH. There was no significant correlation between distinctive microcalcification patterns and the presence of AH or DCIS. There were four patients with a family history of breast cancer in a first degree relative, two of whom had DCIS and two of whom had only AH.

Pathology

Of the 893 patients undergoing SCNB, 221 were found to have hyperplasia without atypia. One hundred thirty-three cases were classified as mild, 36 were moderate and 52 were florid. These patients did not undergo surgical biopsy and were referred for routine follow-up surveillance per American Cancer Society.

As mentioned above, 38 patients were found to have AH and 33 patients went on to surgical biopsy. Five patients elected not to have surgery and were placed in the our risk breast clinic pathway for long term surveillance. With an average follow-up of 24 months, none of the five patients have required repeat core biopsies or been found to have cancer. Carcinoma was discovered in 12 of the 33 patients who proceeded with surgical biopsy. DCIS was present in 11 cases and infiltrating carcinoma in one case. The DCIS was low grade in eight cases, intermediate in two, and high grade in one patient. AH was confirmed at surgical biopsy in 22 of the 33 patients, including seven of the 12 patients with carcinoma. Follow-up of all 28 patients with a primary diagnosis of AH averaged 14 months. Only one of these patients has had repeat core biopsy, and none of these patients had developed breast cancer during the study period.

Ductal vs. Lobular Hyperplasia

When we differentiate between ALH (atypical lobular hyperplasia) and ADH (atypical ductal hyperplasia), ALH was present in seven of 33 SCNB specimens, with four of seven containing both ALH and ADH. Carcinoma was present in two of the seven patients, both of whom had the combination of ALH and ADH on SCNB. Only three of 33 patients were found to have exclusively ALH on SCNB. One was found to have ADH at surgical follow-up while two had ALH.

DISCUSSION

Stereotactic Core Needle Biopsy

SCNB has become an accepted and increasingly popular alternative to open biopsy for early evaluation of suspicious lesions discovered on mammogram. The diagnostic accuracy of SCNB in both benign and malignant disease is well established with histologic agreement to surgical biopsy in over 95% of cases [1,9]. Pettine et al. demonstrated a diagnostic accuracy of 96% for SCNB at our institution. This prior study also determined a positive predictive value of 20% for SCNB in diagnosing malignancies as compared to a positive predictive value of 17%–19% for historical controls referred for wire-guided biopsy prior to implementing the core biopsy program [10].These numbers indicate we are not over utilizing the core biopsy technique and in fact have seen an improvement in our diagnostic capability. Within the study period of March 1993 to July 1996, Madigan completed over 30,000 mammograms and performed 893 core biopsies. Table II lists the stage of breast cancers at the time of diagnosis at Madigan. We have seen a rise in the number of cancers diagnosed as well as an increase in the number of breast cancers at an earlier stage. Comparing our results to the State of Washington as derived from Madigan and the state's tumor registries for the year of 1994, the incidence of in situ cases of breast carcinoma detected for Madigan was 41.1% as compared to 15.2% reported for the state. Additionally, core biopsy is much less invasive for the patients avoiding the risk and inconvenience of open surgical biopsy. These data pro-

TABLE II. Madigan Breast Cancer Pathology: Stage at Diagnosis*

Year	Total	In situ	Local	Regional	Distant	Unknown
1990	61	03	30	24	03	01
1991	54	05	25	21	02	01
1992	55	06	29	18	01	01
1993	68	08	36	20	02	02
1994	73	30	20	16	06	01
1995	73	20	36	16	01	00
1996	72	21	27	23	01	00

*Stereotactic core needle biopsy introduced in March 1993.

vide strong support for the efficacy of SCNB as a diagnostic modality. However significant discordance has been reported in the subgroup of patients with an SCNB diagnosis of AH, and open biopsies have been recommended in this group.

Atypical Hyperplasia

In 1985 Dupont and Page [11] demonstrated the presence of AH in 3.6 % of 10,366 breast biopsies. They further established a fourfold to fivefold increased relative risk of developing invasive cancer in patients diagnosed with ADH or ALH of the breast. Additionally, patients found to have AH and a family history of breast cancer had double the observed risk of developing breast cancer. This has led to recommendations for increased surveillance including periodic mammography in this group of patients. As noted in the methods, AH is diagnosed in those lesions with atypia where complete cytologic and architectural criteria for the diagnosis of DCIS are not present. Additionally, and more relevant to the present discussion, even if all cytologic and architectural criteria for the diagnosis of DCIS are met, but the lesion does not involve at least two spaces, the diagnosis of AH is rendered. It then becomes obvious that when examining a limited specimen such as SCNB, the distinction between AH and DCIS may be difficult, if not impossible, despite strict adherence to established criteria (Fig. 1).

AH was diagnosed in 4.3% of patients undergoing SCNB. Carcinoma was discovered in 36% of patients diagnosed with AH by SCNB, which is in agreement with recent publications (Table III) showing malignancy rates of 33%–87%. There was a notable amount of variability in the rate of malignancies encountered at surgical correlation among the various authors. This is likely twofold in nature. As discussed in Materials and Methods, there is a substantial degree of overlap between the histologic diagnosis of AH and DCIS, making diagnosis more uncertain with a limited sample. Variability among studies in the number of cores taken, the size of the biopsy needle, and the accuracy of stereotactic equipment could potentially alter the diagnostic outcome. A second factor may be the individual institution's experience with stereotactic core biopsies. The studies with a higher percentage of malignancies tended to have fewer total numbers of SCNBs and/or fewer cases of AH, supporting the idea of an institutional learning curve. Despite these differences, all of the studies clearly indicate a need for adjuvant open surgical biopsy in patients with AH diagnosed by SCNB, as well as improved criteria to define those patients in whom an underlying malignancy may be present.

Malignancies were present in patients with both ALH and ADH. As mentioned earlier, Dupont and Page [11] demonstrated an increased risk of carcinoma in patients with either ALH or ADH. In our patient population with only ALH, none of these patients were found to have cancer upon surgical correlation. However, SCNB in two patients demonstrated both ALH and ADH, and these patients were found to have carcinoma at surgical correlation. Additionally one patient with ALH by SCNB was found to have ADH on surgical correlation. Our findings would indicate a similar risk of an associated carcinoma in patients with either ALH or ADH by SCNB. Although our total numbers are small for patients with ALH, based on our findings we continue to support surgical biopsy in both of these subgroups as an adjunct diagnostic procedure to SCNB.

Mammographic Findings

We reviewed the mammograms of all 38 patients with atypical hyperplasia in an attempt to define a characteristic pattern of mammograms which would predict the presence of AH and/or DCIS. Twenty-nine of the patients were found to have suspicious calcifications prompting biopsy. This is in agreement with Helvie et al. and Stomper et al., both of whom found an association of AH with microcalcifications [12,13]. The majority of microcalcifications were pleomorphic in both the AH and DCIS groups. However, beyond the general association of AH and DCIS with microcalcifications, we did not identify specific patterns which would indicate which mammographic lesions would more likely harbor AH or an associated malignancy. This is in agreement with the mammographic review by Moore et al. [5].

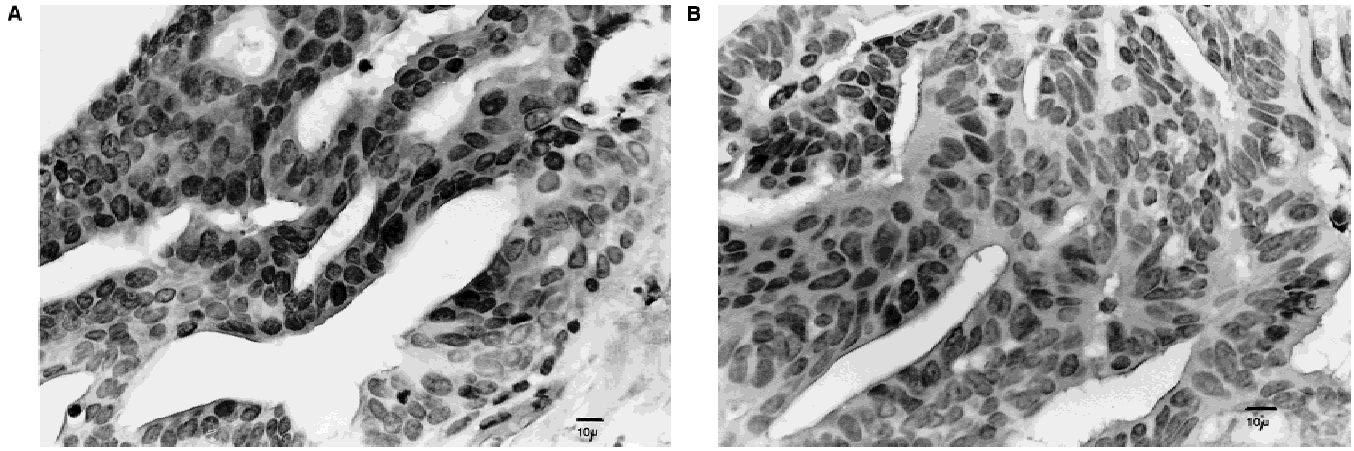

Fig. 1. High magnification views of atypical hyperplasia **(A)** and carcinoma in situ **(B).** Note the similarities in architecture and nuclear detail. The two entities can be indistinguishable on core biopsy specimens encompassing only a portion of the lesion (original magnification ×400).

TABLE III. Literature Review of Surgical Correlation of AH Found by SCNB*

Author	Total SCNBs performed	AH on SCNB	Surgical biopsy with cancer	DCIS	IC
Liberman et al. [3]	264	25/264 (9.5%)	11/21 (52.4%)	8/21 (38.1%)	3/21 (14.3%)
Jackman et al. [2]	450	19/450 (4.2%)	9/16 (56.3%)	6/16 (37.5%)	3/16 (18.8%)
Tocino et al. [4]	358	22/358 (6.1%)	10/22 (45.5%)	5/22 (22.7%)	5/22 (22.7%)
Dahlstrom et al. [6]	206	9/206 (4.4%)	7/8 (87.5%)	6/8 (75%)	1/8 (12.5%)
Moore et al. [5]	510	23/510 (4.5%)	7/21 (33.3%)	7/21 (33.3%)	0/21
This study	893	38/893 (4.3%)	12/33 (36.3%)	11/33 (33.3%)	1/33 (3.0%)
Total	2681	136/2681 (5.1%)	56/121 (46.3%)	43/121 (35.5%)	13/121 (10.7%)

*IC, infiltrating carcinoma; DCIS, ductal carcinoma in situ; AH, atypical hyperplasia; SCNB, stereotactic core needle biopsy.

Ductal Carcinoma In Situ

The majority of malignancies present were DCIS. Only one of the DCIS lesions in our study was high grade. The remaining ten lesions had more favorable histology. In the study by Moore et al. [5], two of seven DCIS lesions were found to be high grade in general agreement with our findings. The high incidence of an associated malignancy in patients with AH by SCNB may represent a sampling error or concurrent disease. Seven of the eleven cases of DCIS were also found to have AH on open biopsy. This finding supports the idea that the DCIS and AH represent concurrent lesions or progression of disease. If this were a sampling error, then we would expect a decline in the incidence of associated malignancies if we increase the size of our sampling needle. We are presently conducting a prospective study using an 11-gauge suction-assisted mammotome needle to determine if there is a decreased incidence of DCIS associated with AH at core biopsy as we increase the sample size. These results are pending.

There has been a steady decline in the number of DCIS lesions treated with mastectomy and a concomitant rise in conservative therapy. Presently, 30%–50% of patients with DCIS are being treated with lumpectomy alone or in combination with radiation therapy [14]. Our present study demonstrates that the majority of these lesions are low grade with favorable histology. This knowledge of the predominant associated malignancy in patients with AH serves as a guide for surgical biopsy. There exists a potential for both diagnostic and therapeutic excisional biopsy of carcinoma as a single surgical procedure. We would therefore recommend that adjunct surgical biopsy of AH lesions be approached with generous margins in light of the high prevalence of an associated low grade malignancy.

All patients with a primary diagnosis of AH have been followed in our high risk breast clinic including the five patients who did not undergo surgical biopsy. None of the patients have been found to have malignancy to date with an average follow up for the group of 1 year. In regard to those patients who had an SCNB diagnosis of AH but who did not undergo surgical biopsy, we have not routinely recommended follow up SCNB of prior AH lesions in these patients unless there is a change in their mammogram prompting biopsy. These patients have been followed for 2 years without evidence of malignancy. We continue to urge consideration for surgical biopsy in all patients with a SCNB diagnosis of AH.

Additionally, we continue to recommend increased surveillance of those patients with a primary diagnosis of AH by SCNB or surgical biopsy.

CONCLUSIONS

SCNB is an accurate diagnostic modality for most breast lesions; however, there is a high incidence of DCIS not detected in women diagnosed with AH. Greater than a third of these patients harbor an associated malignancy. The majority of the malignancies present are DCIS of favorable histology. We have noted no identifiable mammographic criteria to characterize which patients may have a malignancy. We recommend open biopsy on all patients with AH diagnosed by SCNB. This procedure should be conducted as a standard lumpectomy to obtain negative margins and possibly circumvent the need for further surgical intervention in this cohort of patients.

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